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Biopsychosocial risk factors of persistent fatigue after acute infection: a systematic review to inform interventions.

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Key words: Fatigue, Risk factors, Biopsychosocial, Post-infection, Systematic review, Narrative synthesis

Abbreviations

CFS: Chronic Fatigue Syndrome

IM: Infectious Mononucleosis

RRV: Ross-River virus

GP: General Practitioner

N: Number

CDC: Centre for Disease Control and Prevention

Abstract

Objectives

Fatigue is a prevalent and debilitating symptom, preceded by an acute infectious episode in some patients. This systematic review aimed to identify risk factors for the development of persistent fatigue after an acute infection, to develop an evidence-based working model of post-infectious fatigue.

Methods

Electronic databases (Medline, PsycINFO and EMBASE) were searched, from inception to March 2016, for studies which investigated biopsychosocial risk factors of on-going fatigue after an acute infection. Inclusion criteria were: prospective design; biological, psychological or social risk factors; standardised measure of post-infectious fatigue (self-report scales or clinical diagnosis). Studies were excluded if the sample had a pre-existing medical condition, infection was conceptualised as 'vaccination' or they were intervention trials. A narrative synthesis was performed.

Results

Eighty-one full texts were screened, of which seventeen were included in the review. Over half included glandular fever populations. Other infections included dengue fever, 'general'/'viral' and Q-fever. Risk factors were summarised under biological, social, behavioural, cognitive and emotional subthemes. Patients' cognitive and behavioural responses to the acute illness, and pre-infection or baseline distress and fatigue were the most consistent risk factors for post-infectious fatigue.

Conclusion

An empirical summary model is provided, highlighting the risk factors most consistently associated with persistent fatigue. The components of the model, the possible interaction of risk factors and implications for understanding the fatigue trajectory and informing preventative treatments are discussed.

Introduction

Fatigue is a commonly reported symptom. Every year 1.5% of the UK population present to the GP with tiredness or fatigue as a new symptom (Gallagher et al., 2004) and between 5-7% of people attending primary care present with a primary complaint of fatigue (Hamilton et al., 2010).

Around half of people with tiredness/fatigue as a major or concurrent symptom recover within one year (Nijrolder et al., 2008a, Nijrolder et al., 2008b). However, for some, fatigue persists for over six months, which is then defined as chronic (O'Halloran et al., 2004, Centers for Disease Control and Prevention (CDC), 2012). If more stringent criteria are met, including fatigue that is disabling in nature, a diagnosis of chronic fatigue syndrome (CFS) may be made (Sharpe et al., 1991, NICE, 2007, CDC, 2012). A recent review suggests the prevalence of clinically assessed CFS is approximatley 0.76% of the population (Johnston et al., 2013).

A number of precipitants or triggers have been associated with chronic fatigue, but no clear cause has been found (Lorusso et al., 2009). One common precipitant is moderate to severe, infectious viral illness, including infectious mononucleosis (IM)/glandular fever, Ross-River virus (RRV) and Coxiella burnetti (Q-fever) (Ayres et al., 1998, Kondo, 2006, Hickie et al., 2006). However, the majority of people experiencing these infections do recover, suggesting that acute infection may be a 'necessary but insufficient cause' (White, 2007; p4). Current guidelines advocate tiredness/fatigue management in primary care by identifying and addressing relatively broad 'modifiable psychological, social, and general health factors' (NICE, 2015). However, it is currently not known which specific factors should be targeted. Summarising the current evidence of modifiable risk factors which interact with infection to maintain or perpetuate post-infectious fatigue may provide clearer guidance for treatment.

A review by Candy et al. (2002) investigated clinical and psychological variables associated with recovery after IM and found that poor physical functioning predicted prolonged ill health, whilst evidence for symptom-related and psychological risk factors (mood disorder and personality) was mixed. The review, however, focused exclusively on IM and a number of prospective infectious studies have been published since this date. Additionally, the outcome was broadly defined as 'recovery' rather than persistent fatigue, for example, absence of persistent symptoms and psychological well-being. This could account for some of the inconsistent findings reported.

A more recent scoping review identified a large number of heterogeneous risk factors associated with the onset of CFS. These ranged from childhood trauma and mood disorder, to

family members with CFS and recent ingestion of raw milk (Hempel et al., 2008). This review only included studies measuring clinically defined CFS, potentially missing risk factors of more general, persistent fatigue. Additionally, the studies included did not necessarily focus on post-infectious fatigue and 'did not appear to reveal risk factors that are evidently useful for clinicians' by being potentially modifiable (Hempel et al., 2008, p924). Although fatigue can be precipitated by a range of factors, post infectious chronic fatigue may provide a more homogenous group to study (Fukuda et al., 1994). Therefore, the primary aim of this systematic review was to identify biopsychosocial risk factors associated with persistent fatigue post-infection across the fatigue trajectory, which are potentially modifiable. Unmodifiable demographic factors such as gender were beyond the scope of the review. The secondary aim was to summarise the empirical findings in a theoretical model to guide development of early interventions to treat post-infectious fatigue.

Methods

Search strategy

The databases Medline, PsycINFO and EMBASE were searched from inception to March 2016. The search strategy combined MeSH terms and key-words relating to fatigue, predictive design and infection (see Appendix A for full search strategies). Relevant grey literature was identified by contacting experts in the field and searching OpenGrey. The reference lists and citations of included studies were also hand-searched.

Study selection

Table 1 provides the overview of inclusion and exclusion criteria for studies. KH screened titles and abstracts and two authors (KH, PR) screened full-texts. Any uncertainties about study inclusion were resolved with the wider research team.

Table I

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Prospective study design	Intervention trials.
Patients who had experienced an acute (short-term, non-chronic) infection confirmed by a doctor or laboratory test.	The patient sample had a pre-existing medical condition.
Assessed the presence of fatigue at a stated follow-up time-point following the infectious episode.	The patient sample was already chronically fatigued at baseline.
Reported quantitative and empirical data investigating risk factors of fatigue.	The infection was conceptualised as 'vaccination'.
Measured fatigue outcome using a valid and reliable self-report tool or diagnosis by a medical professional according to international diagnostic guidelines (Fukuda et al., 1994, Sharpe et al., 1991) or professional clinical opinion at follow-up.	
Measured biological, psychological, social or emotional risk factors, either before the onset or at the time of acute infection (not demographics).	

Data Extraction

The following information was independently extracted by KH and PR; infection characteristics, sample demographic characteristics, study design, statistical methods, risk factors, fatigue measure and follow-up time-points, and the statistical outcomes. Where relevant analyses were missing authors were emailed to request statistical results but responses were not received (N=3). Both univariate and multivariate results were extracted, but univariate findings were prioritised during synthesis to enable comparability across studies where possible.

Assessment of within study risk of bias and study quality

The methodological quality and risk of bias of included studies was assessed using The Effective Public Health Practice Project Quality Assessment Tool (Armijo-Olivo et al., 2012). The tool rates studies on selection bias, study design, confounding variables, blinding, data collection and degree of withdrawal. The tool was modified to better assess observational studies, based on other tools (Downs and Black, 1998, Wells et al., 2000) (see Appendix B). We explored whether quality assessment domains could account for heterogeneity in review findings, according to recommendations by Reeves et al. (2008).

Methods of Analysis

The wide range of risk factors and fatigue measurement methods ruled out a meta-analysis. Therefore, narrative synthesis was used, identifying themes among risk factors (Popay et al., 2006).

To provide meaningful comparison, risk factor data were extracted in categories according to fatigue time scales and definitions. Current guidelines suggest categorising fatigue according to three time periods following acute infection; <=3 months, 4+ months, and 12+ months (NICE, 2015). Accordingly, we classified fatigue as i) sub-acute, ii) chronic and iii) long-term, respectively. Within the 'chronic' grouping a distinction was made between studies using diagnostic criteria (e.g. Oxford (Sharpe et al., 1991) and/or CDC criteria) to define 'CFS' and those measuring the presence of 'chronic fatigue' using self-report.

The review was conducted in accordance with PRISMA guidelines (Moher et al., 2009).

Results

Study Characteristics

The search returned 1,850 citations, of which 78 full texts were retrieved after screening titles and abstracts. Three full texts were identified from other sources. Eighteen articles met inclusion criteria. Study characteristics, including fatigue measures/criteria used, are detailed in Appendix C. Acute infections included IM (N=9), Q-fever, Ross-River virus (or a combination of the three), dengue fever, viral meningitis and shiga toxin-producing Escherichia coli 0104 (STEC) infection. Three studies investigated populations with 'general' or 'viral' infections. A range of follow-up time-points were used but six months (chronic) was the most common (N=11). The number of participants ranged from 71 to 2327, and mean ages fell between 16.09 years and 48.50 years.

Three papers used the same cohort (Katz et al., 2009, Huang et al., 2010, Jason et al., 2014). As each of these papers reported different risk factors all were included in this review. Two papers reported anxiety and depression in different analyses for the same cohort of IM patients (Moss-Morris & Spence, 2006, Moss Morris et al., 2011); only data from the 2011 publication were included here and the 2006 publication was excluded. One study (Cope et al., 1996) included participants recruited from a previous cohort (Cope et al., 1994), with the addition of a healthy control group. The two papers were considerably different though; Cope et al. (1994) included more participants, used a cohort design and focussed on chronic fatigue, whereas Cope et al. (1996) focused on CFS and included controls. Therefore, both were included. In total, 17 papers are included in this narrative synthesis (see Figure 1).

Insert Figure 1 here

Grouping of risk factors

Significant risk factors were grouped under five component themes (biological, social, behavioural, cognitive and emotional), with sub-themes where applicable. These risks factors are summarised in Figure 2, with more details by theme and fatigue time-point (sub-acute, chronic and long-term) in tables 3-7 (Appendix D). Factors in bold in Figure 2 were the ones most consistently related to fatigue, either across time points and/or in multiple studies. Other variables were only associated with fatigue at certain time points. Variables found not to be risks for fatigue in any studies are listed in table 2 and, for the sake of brevity, are not included in the synthesis.

Insert Figure 2 here

Table 8 (Appendix E) summarises the ratings for each study across the quality domains, with studies rated as weak, moderate or strong. Of the quality domains assessed, ratings between studies differed particularly for ‘confounders’, ‘data collection’ and ‘withdrawal’. Where there were discrepant findings across studies in relation to risk factors and fatigue outcomes, we explored whether study quality, sample characteristics or infection characteristics could account for these.

Table II

Measured variables which were not shown to be significant predictors of fatigue at any time-point.

Biological	Social	Behavioural	Cognitive	Emotional
Haemotological and biochemical parameters *Inflammatory markers* White cell count (Seet et al., 2007) IL-6 levels and CRP levels (Kremers et al., 2014) *Stress markers* Cortisol - baseline AUC values, Cortisol - change in AUC (baseline to six months) (Candy et al., 2003) *General markers* (Concentrations of…) haemoglobin, haematocrit, platelet, sodium, potassium, urea, creatinine (Seet et al., 2007) Liver (among other) functions (Concentrations of…) albumin, total bilirubin, alkaline transaminase, alkaline phosphatase, lactate dehydrogenase, prothrombin time, activated thromboplastin time (Seet et al., 2007) yGT at 1 month, Bilirubin at 1 month (White et al., 2001) **Symptoms at time of infection** Acute sickness (Hickie et al., 2006) Fever, Nausea, Poor appetite, Cough, Abdominal pain, Vomiting Diarrhoea, Headaches (Seet et al., 2007) Neurological symptoms, 4+ instances of diarrhoea on 3+ days Abdominal pain, Length of bloody diarrhoea, Fever (Löwe et al., 2014) **Medication during acute phase** Steriod therapy during acute phase (Katz et al., 2009) Medication (antibiotic prescription) (Cope et al., 1994) **Previous symptoms** Premorbid atopy (Petersen et al., 2006) Diarrhoea in past 4 months (Löwe et al., 2014) **Comorbid syndromes** Hemolytic uremic syndrome (Löwe et al., 2014) Atopy (White et al., 2001) **Weight** Weight at baseline, Weight change over six months (Schur et al., 2008)	**Doctor's advice** … to rest (Moss-Morris et al., 2011, Candy et al., 2003). … to avoid exercise … to take medication (e.g. paracetamol) (Moss-Morris et al., 2011) Sickness certificate in the year before IM (Petersen et al., 2006) **Family influence** Family stress at or prior to onset Family stress at or prior to onset continuing Family stress since mononucleosis Family stress since mono continuing (Jason et al., 2014) Family psychiatric history (Cope et al., 1996) Childhood experience of illness in family (Candy et al., 2003) Perceived social support (Löwe et al., 2014)	**Exercise** Exercise power (White et al., 2001) Does regular sport (Candy et al., 2003) **Physical activity** Physical and sedentary activities pre-infection and at baseline: 20-Minute hard exercise, 20-Minute light exercise, television/video/computer, sleep, napping, other sedentary activity (Huang et al., 2010)	**Individual traits** Self- rated extroversion Relative-rated extroversion (White et al., 2001) Pessimism Optimism (Löwe et al., 2014) **Illness beliefs** Believing fatigue had a physical cause at presentation (Wessely et al., 1995) General beliefs about viruses (combination of perception of personal vulnerability to viruses, attribution of ill health to viruses and general beliefs about prevention and treatability of viral illness) (Cope et al., 1994) **Other** Locus of control (internal versus external) (Hickie et al., 2006) Self-efficacy Fear of death (Löwe et al., 2014)	**Symptoms at time of infection** Mood disturbance (Hickie et al., 2006)

Biological factors

Haemotological and biochemical parameters

A large number of biological markers were assessed (see table 2 for non-significant biological risks), but only three appear to be significant risk factors. During infection, higher percentage of activated CD4 (helper) and CD8 (cytotoxic) t-cells (Candy et al., 2003) and aspartate transaminase concentration (a measure of liver inflammation) (White et al., 2001), were risk factors for sub-acute fatigue, although aspartate transaminase concentration was not significant in multivariate analyses (controlling for demographics, symptoms, laboratory and dengue severity covariates) in a less representative (hospital inpatient) dengue fever sample (Seet et al., 2007).

Aspartate transaminase concentration was also a risk for more broadly defined chronic fatigue but not CFS (White et al., 2001). Activated CD4 and CD8 percentages were not risk factors for chronic fatigue or CFS (Candy et al., 2003).

Individual symptoms

A wide range of symptoms reported at the time of infection were investigated as risk factors for fatigue. Fatigue reported at the time of acute infection was a risk factor for sub-acute fatigue in an IM (White et al., 2001) and a combined IM, Q-fever, RRV sample (Hickie et al., 2006), but not in a dengue fever, inpatient sample (Seet et al., 2007). Other symptoms shown to be risks for sub-acute fatigue included lymphadenopathy (White et al., 2001), irritability, musculoskeletal pain, neurocognitive disturbance (Hickie et al., 2006), and presence of chills (Seet et al., 2007). A methodologically weaker study broadly measuring fatigue 'in the year after onset', reported lymphadenopathy was not associated with sub-acute fatigue (Petersen et al., 2006).

Of these symptoms, fatigue and musculoskeletal pain remained significant risk factors for chronic fatigue (White et al., 2001) and CFS (Cope et al., 1996, Hickie et al., 2006, Huang et al., 2010). Autonomic symptoms were also a risk factor for CFS (Jason et al., 2014).

In the only study to assess symptoms in relation to long-term fatigue only fatigue during infection was a significant risk (Hickie et al., 2006).

Severity of acute symptoms

Self-reported severity of general somatic symptoms was a risk factor for sub-acute fatigue in an IM sample (Candy et al., 2003) but objectively rated dengue fever severity was not (Seet et al., 2007).

Self-reported severity of symptoms was not associated with chronic fatigue (Wessely et al., 1995, Candy et al., 2003), and neither was duration of inpatient care for STEC infection (Löwe et al., 2014). However, treatment in intensive care for STEC infection was associated with chronic fatigue (Löwe et al., 2014).

Self-reported severity of symptoms was associated with long-term fatigue in the only study to assess this time-point (Candy et al., 2003).

Number of acute symptoms

Three studies investigated overall number of self-reported symptoms (Wessely et al., 1995, Candy et al., 2003, Moss-Morris et al., 2011). Number of general somatic symptoms was a risk factor for sub-acute fatigue in both IM studies to measure this (Candy et al., 2003, Moss-Morris et al., 2011). However, the number of IM-specific symptoms was not significantly associated with sub-acute fatigue (Moss-Morris et al., 2011).

The number of general somatic symptoms was also a risk factor for chronic fatigue in one of two studies (Wessely et al., 1995) and for CFS (Moss-Morris et al., 2011), but number of infection specific symptoms was not a risk factor for chronic fatigue (Wessely et al., 1995, Moss-Morris et al., 2011).

High total number of symptoms was significantly related to long-term fatigue in the only study assessing this time-point (Candy et al., 2003).

Pre-existing health issues

Petersen et al. (2006) reported that pre-infectious fatigue was associated with sub-acute fatigue. In terms of chronic fatigue, pre-morbid fatigue was a risk factor in a higher quality, large community study (Wessely et al., 1995) but not a smaller, primary-care study (Cope et al., 1994). More general, pre-existing (chronic) health problems were associated with both chronic fatigue (Löwe et al., 2014), and long-term fatigue (van Loenhout et al., 2015).

Social factors

Adverse events

Prior adverse events in the past year (e.g. parents divorcing or separating) were a risk factor for CFS in adolescents (Jason et al., 2014), but not for sub-acute, chronic or long-term fatigue after IM (Candy et al., 2003) or sub-acute fatigue after STEC infection (Löwe et al., 2014) in adults.

GP interactions

Sick certification related to the acute infection was a risk factor for chronic fatigue (Cope et al., 1994) and CFS (Cope et al., 1996), as was uncertain diagnosis of viral illness (Cope et al., 1994).

Behavioural factors

All-or-nothing behaviour

One study found all-or-nothing behaviour, i.e. pattern of over-activity followed by the need to rest up and recover at the time of acute infection, was a risk factor for both sub-acute fatigue and CFS (Moss-Morris et al., 2011).

Limiting behaviour

Bed-rest during the illness (i.e. number of days in bed) was a risk factor for sub-acute fatigue (White et al., 2001), whereas self-reported limiting behaviour (i.e. reduction or avoidance of activity) (Moss-Morris et al., 2011) and being off work for more than 10 days (Candy et al., 2003) were not.

Bed-rest (White et al., 2001, Jason et al., 2014) and days off school (Jason et al., 2014) were risk factors for CFS but, once again, self-reported limiting behaviour and being off work were not associated with CFS (Moss-Morris et al., 2011) or chronic or long-term fatigue (Candy et al., 2003).

Previous GP attendance

The number of GP consultations in the year prior to illness was a risk factor for sub-acute fatigue in one study broadly defining fatigue 'in the year after onset' (Petersen et al., 2006) but not in another using a defined time-point of 2 months (White et al., 2001). Prior GP consultations were also a risk factor for CFS, but not chronic fatigue (White et al., 2001).

Functioning and fitness

A few different operationalisations of functioning and fitness were investigated. Impaired general functioning and poor physical functioning in the month prior to and during infection, were risk factors for sub-acute fatigue (Candy et al., 2003). Conversely, better physical fitness at baseline (objectively measured using a step test) was associated with a reduced risk of sub-acute fatigue (White et al., 2001).

Of these variables, only physical fitness was associated with reduced risk of chronic fatigue and CFS (White et al., 2001). School based functioning was not associated with CFS in adolescents (Jason et al., 2014).

In the one study which looked at long-term fatigue, only impaired general functioning was a risk factor (Candy et al., 2003).

Cognitive factors

General individual differences

Perceived stress

Jason et al. (2014) found that perceived stress was related to CFS in adolescents but Moss-Morris et al. (2011) did not find the same relationship in adults. Both studies reported univariate analyses, investigated IM and were of good quality across each of the domains assessed.

Negative perfectionism

Moss-Morris et al. (2011) reported that 'negative perfectionism', i.e. striving to achieve high goals to avoid negative consequences (Slade and Owens, 1998), was a risk factor for CFS, but not sub-acute fatigue.

Attributional style

Somatising (attributing symptoms to physical illness) and absence of normalising (attributing symptoms externally to situational or environmental factors) were risk factors for chronic fatigue (Cope et al., 1994). A psychological attribution style (attributing symptoms internally to emotional distress) was a risk factor for both chronic fatigue (Cope et al., 1994) and CFS (Cope et al., 1996).

Neuroticism

Neuroticism (also conceptualised as self- or relative-rated emotionality (White et al., 2001)) was not a risk factor for sub-acute fatigue (Hickie et al., 2006, White et al., 2001). It was related to chronic fatigue after STEC infection (Löwe et al., 2014) and CFS in an IM sample (White et al., 2001) but not a combined IM, Q-fever, RRV sample (Hickie et al., 2006). In the one study using a long-term fatigue follow-up, neuroticism was not associated with long-term fatigue (Hickie et al., 2006).

Illness specific perceptions

Various dimensions of patients' beliefs about their illness were investigated in two IM studies: identity beliefs (patients' attribution of general somatic symptoms to their acute infection) (Moss-Morris et al., 2011), prolonged recovery beliefs, and perceiving more serious illness consequences were all risk factors for sub-acute fatigue (Moss-Morris et al., 2011, Candy et al., 2003). Low personal control beliefs were a risk factor for sub-acute fatigue in one of these two studies (Moss-Morris et al., 2011). Conversely, higher coherence (how much someone feels they understand their acute illness) significantly reduced the risk of sub-acute fatigue, effectively acting as a protective factor (Moss-Morris et al., 2011). Interestingly, no studies found attributing the illness to a virus was a risk factor.

Of these illness beliefs, prolonged recovery beliefs remained a risk factor for chronic fatigue (Candy et al., 2003) and CFS (Moss-Morris et al., 2011). Believing the infection to have serious consequences was also still a risk for chronic fatigue (Candy et al., 2003) but not CFS (Moss-Morris et al., 2011). Moss Morris et al.'s (2011) study received a higher quality rating because of its larger sample size and fewer dropouts. Higher coherence was again protective in relation to CFS (Moss-Morris et al., 2011).

None of the illness beliefs were risk factors of long-term fatigue in the one study with this follow-up time-point (Candy et al., 2003).

Emotional factors

Anxiety

Anxiety was investigated in two IM studies (White et al., 2001, Moss-Morris et al., 2011). It was a risk factor for sub-acute fatigue in one of these (Moss-Morris et al., 2011). Both studies found anxiety to be a risk factor for CFS, but not chronic fatigue (Moss-Morris et al., 2011, White et al., 2001).

Depression

Depression at baseline was investigated in the same two studies. Only one of these found it to be a risk for sub-acute fatigue and CFS (Moss-Morris et al., 2011), although White et al. (2001) reported it was a risk factor for chronic fatigue.

Distress

Five studies focused on psychological distress; either general or illness related (negative perceptions of the emotional impact of symptoms).

General (Candy et al., 2003) and illness related (Moss-Morris et al., 2011) distress were both risk factors for sub-acute fatigue. General distress was also a risk factor for chronic fatigue (Cope et al., 1994, Wessely et al., 1995, Candy et al., 2003), but not CFS (Cope et al., 1996), although no data was provided to support the latter finding. Illness related distress was associated with CFS (Moss-Morris et al., 2011).

In the only study measuring long-term fatigue, general distress was not a risk factor (Candy et al., 2003).

Psychiatric diagnosis

Psychiatric diagnosis at the time of infection was not related to sub-acute fatigue (Hickie et al., 2006).

In terms of CFS, psychiatric diagnosis was a risk factor in univariate analyses of an adolescent IM cohort (Jason et al., 2014) but not in multiple regression analyses of an adult, combined IM/Q-fever/RRV cohort (Hickie et al., 2006). Psychiatric diagnosis at time of infection was not associated with long-term fatigue (Hickie et al., 2006).

Premorbid (pre-infection) distress

A large number of operationalisations of premorbid distress, including the presence of pre-morbid mood disorder, psychiatric disorder (interview and GP record of disorder/treatment) and emotional problems were measured in eight studies.

Premorbid emotional risk factors for sub-acute fatigue were investigated by four studies (White et al., 2001, Candy et al., 2003, Hickie et al., 2006, Petersen et al., 2006). Of these, only one study (the weakest on the data collection quality domain) reported an association with sub-acute fatigue (Petersen et al., 2006).

In terms of chronic fatigue, only two of the 14 pre-morbid distress measures (across four studies) were risk factors: GP record of pre-morbid mood disorder (White et al., 2001) and psychological morbidity during community sampling (Wessley et al., 1995).

In terms of CFS, five of the 11 investigated variables (across 3 studies) were shown to be risk factors, all in White et al.'s (2001) study.

Premorbid distress, conceptualised as 'psychiatric history from case-notes', was a risk factor for long-term fatigue in one study with a broad follow-up period of 6-24 months (mean=18) (Hotopf et al., 1996), whereas it was not a risk at 12 months in two studies, when conceptualised as previous psychiatric disorder (diagnostic interview) (Hickie et al., 2006) or emotional problems (questionnaire) (Candy et al., 2003).

Discussion

Risk factors of persistent fatigue after acute infection varied depending on follow-up time-point and fatigue outcome definition. Despite this heterogeneity, there were some patterns in the data where variables were either risks for fatigue across time-points and/or definitions, or multiple studies reported that a particular variable was a risk factor. These factors are summarised in Figure 2. Across all infection types, 'distress' and 'fatigue at time of infection' were significant risk factors for chronic fatigue. Other variables were only significantly associated with persistent fatigue at certain time points, suggesting that the significance of some risk factors may differ across the trajectory of sub-acute, chronic and long term fatigue.

Biological factors, including CD4, CD8 and aspartate transaminase biomarkers and a range of infectious symptoms, largely appeared to be significant risk factors for sub-acute rather than chronic fatigue. The increased percentage of activated CD4 and CD8 suggests an altered inflammatory response, whereby the immune system is chronically activated (Lorusso et al., 2009). Chronic activation may also produce more severe infectious symptoms. This is in

line with the findings that infectious symptoms such as lymphadonophathy, fatigue and pain were also risks for sub-acute fatigue.

Risk factors for fatigue across multiple time-points were patients' cognitive and behavioural responses to their illness and symptoms, tendency to report a wide range of somatic symptoms when acutely ill, distress at time of infection (both general and illness related), and fatigue (both pre-morbid and at time of acute infection). Physical fitness at baseline reduced risk of fatigue post-infection. Findings for premorbid psychiatric diagnosis were more mixed. There were more negative than positive results in this area, suggesting that whilst chronic fatigue is related to distress it is less likely to be a sequelae of a mental health disorder.

Sick certification and longer bed-rest at the time of infection were also associated with chronic fatigue and/or CFS. These risks could represent more severe infection or inflammatory responses and general ill health. On the other hand, they may represent generalised illness worry, reflected in the cognitive behavioural risks for fatigue across the six-month trajectory. These include the tendency to attribute symptoms to either psychological or physical illness rather than normal events, and to view illness and symptoms as chronic, serious and difficult to understand. The key self-reported behavioural risk was a pattern of boom and bust (all-or-nothing) whereby patients overdo things on days they feel better and then have prolonged periods of needing to rest up as a consequence (Surawy et al., 1995). Only one study included this behavioural variable, so conclusions must be tentatively drawn.

Finally, although retrospective reporting suggests previous stressful events precede CFS (Hatcher & House, 2003, Nater et al., 2011), the prospective findings for the role of prior stressful or adverse events were mixed, with only one of three studies (focused on adolescents) showing a significant association with fatigue (Jason et al., 2014). It may be that an individual's feelings of stress or distress or an accumulation of daily hassles and pressures (rather than the occurrence of specific stressful events) are risk factors for ongoing fatigue, i.e. the subjective experience of stress levels (Nater et al., 2011). One study found that high personal standards (negative perfectionism) was associated with CFS which is in line with subjective feelings of falling short of self-imposed standards (Moss-Morris et al., 2011).

All the prospective studies reviewed investigated simple linear associations between these biopsychosocial factors and persistent post-infection fatigue. However, existing theoretical models of persistent physical symptoms propose predisposing, precipitating and perpetuating risk factors which interact to create a vicious cycle of physical symptom maintenance (Deary et al. 2007, Moss-Morris et al., 2012). Drawing from and incorporating these theories, we present a hypothetical model of fatigue which illustrates how the risks factors

identified in this review may interact to maintain a vicious cycle of fatigue after infection (see Figure 3).

Pre-existing health issues and fatigue, lack of fitness and distress/stress may be predisposing factors for post-infectious fatigue. When individuals with one or more of these vulnerability factors are exposed to an infection this may precipitate a heightened immune response and more severe acute symptoms. In turn, this may result in increased bed-rest, sick certification and time off work (prolonged inactivity). In response, people may push quickly to get back to previous levels of activity only to find this 'boom' behaviour produces further symptoms. If these symptoms are attributed to a psychological or physical illness, rather than normalising these in relation to pushing too hard after a time of bed-rest or severe symptoms, patients may develop a negative representation of symptoms. The response may be to rest again (bust behaviour) rather than risk activity. This in turn produces more symptoms and an ongoing vicious cycle. Future research exploring interactions between these factors is needed to validate this model.

Insert Figure 3 here.

Clinical Implications

As prolonged bed-rest, sick certification and all-or-nothing behaviour are associated with persistent fatigue, careful guidance about gradual return to work and activity may be more useful than suggesting patients should rest (Candy et al., 2002). Reducing the chance of physical deconditioning is important given findings that individuals with IM in a constrained activity condition took significantly longer to recover than those whose activity was unrestricted (Dalrymple, 1964).

The evidence of cognitive behavioural factors and poor illness coherence as risk factors of post-infectious fatigue illustrates the importance of providing clear, explanatory models to patients, including the fact that prolonged symptoms may not necessarily relate to the original infection. It also highlights the potential for simple behavioural interventions to enhance post-infection recovery, as demonstrated by a small, pilot randomised control trial targeting gradual return to activity in IM patients (Candy et al., 2004).

Strengths and limitations of the review

By focusing on prospective studies, this review allows greater confidence in directional relationships and identifies findings that could be relevant for persistent fatigue prevention.

Whilst some studies undertook analyses controlling for certain variables, others did not. Where possible we extracted results relevant to the simplest, uncontrolled data analyses to promote comparability and decrease heterogeneity across studies. However, as some did control for possible confounds, this may have led to mixed findings in some areas.

Importantly, the proposed model is constrained by the findings reported. Conclusions cannot be drawn about factors which have not been measured. Similarly, we cannot conclude which risk factors are 'most important'. We looked for consistency across studies and/or time-points and highlighted these factors in Figure 2. However, the variety of individual factors included, and importantly their inclusion in only one or two studies, limits the weight that can be assigned to these findings. Thus, it is important to stress that Figure 2 should only be viewed as a summary of this review's findings in parallel with tables 3-7, as opposed to a definite model of the perpetuation of chronic fatigue. Therefore, although potential risk factors for persistent post-infectious fatigue have been highlighted by this review, these associations require further replication to confirm their role, particularly as the heterogeneity amongst findings could be accounted for by multiple factors: sample characteristics, clinical characteristics, level of analysis or study quality. The extent of the involvement of these factors requires clarification.

Future research

Most prospective studies explored linear relationships between persistent fatigue and a few risk factors in a clinical population, without specifying a theoretical model. Few used community sampling and none explored the possible interaction between risk factors. Using a defined model to choose risks factors in future work, and doing so within a large longitudinal sampling frame, will help build knowledge of the complex interaction of factors likely to be associated with fatigue after infection. More consistent control of possible confounders (e.g. age and gender) across studies would also allow for more direct comparison between studies. Investigating the interaction with other physiological variables associated with chronic fatigue such as decreased cortisol secretion, postural orthostatic tachycardia and microbiome abnormalities may help elaborate the biological parameters underpinning persistent fatigue (Powell et al., 2013, Lewis et al., 2013, Giloteaux et al., 2016).

In conclusion, the evidence and model presented are dependent on studies' focus and methodology. Caution is advised when drawing conclusions about risk factors measured by a small number of studies. Despite the heterogeneity, certain variables were shown to be significantly associated with persistent fatigue across multiple studies and/or across the six-month fatigue trajectory, many of which encompassed aspects of patients' responses to illness. These modifiable psychosocial risk factors lend themselves to future early interventions to manage sub-acute, post-infectious fatigue.

Figure captions

Figure 1: Flow diagram detailing study inclusion and exclusion.

Figure 2: A summary of the biopsychosocial variables shown to be potential risk factors for persistent post-infectious fatigue up to six months.

Note*: Risk factors in **bold are those factors that were associated with persistent fatigue across time-points in the six-month trajectory, or those which were duplicated across studies. Those not in bold were mixed findings. Such discrepancies could be explained by different infectious illnesses, study characteristics (e.g. sample size, sample population, quality), statistical analyses (e.g. univariate versus multivariate), measures used (e.g. self-report versus objective measures) or fatigue measurement factors (e.g. definition, time-point). Evidence for risk factors marked with ˜ was very variable.

Figure 3: A hypothetical vicious cycle of interacting risk factors for fatigue.

Appendices

Appendix A: Search terms
Appendix B: Quality assessment tool
Appendix C: Study characteristics
Appendix D: Overview of risk factor groupings by fatigue time point (Tables 3-7).
Appendix E: Summary of ratings for each study across the quality domains (Table 8).

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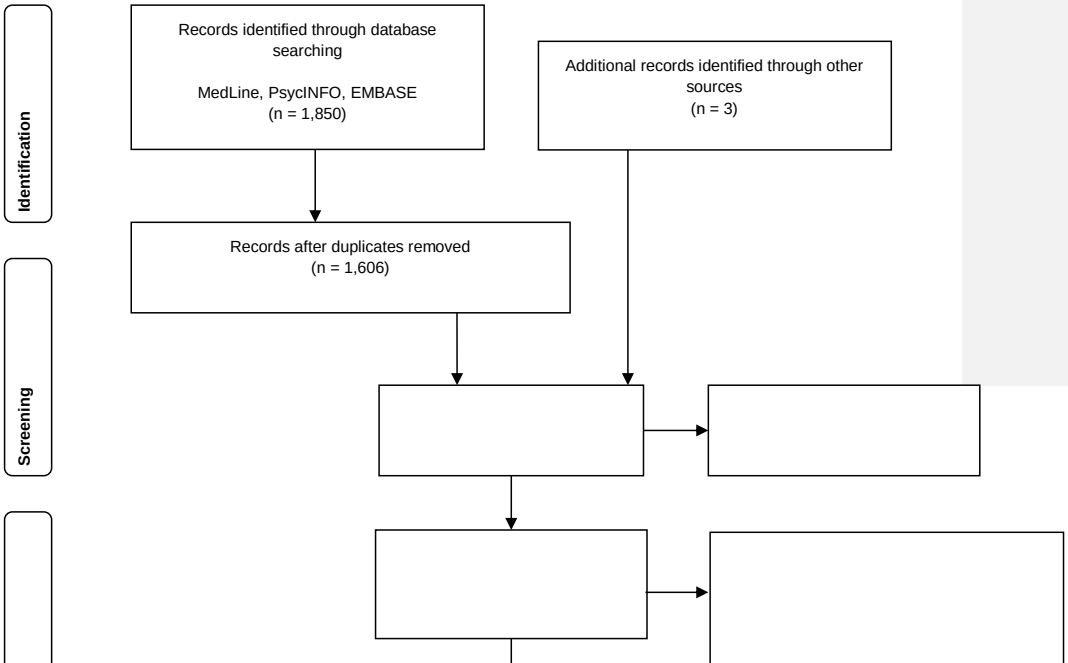
Identification
Screening
Records identified through database searching
MedLine, PsycINFO, EMBASE
(n = 1,850)
Additional records identified through other sources
(n = 3)
Records after duplicates removed
(n = 1,606)

Figure 1: Flow diagram detailing study inclusion and exclusion.

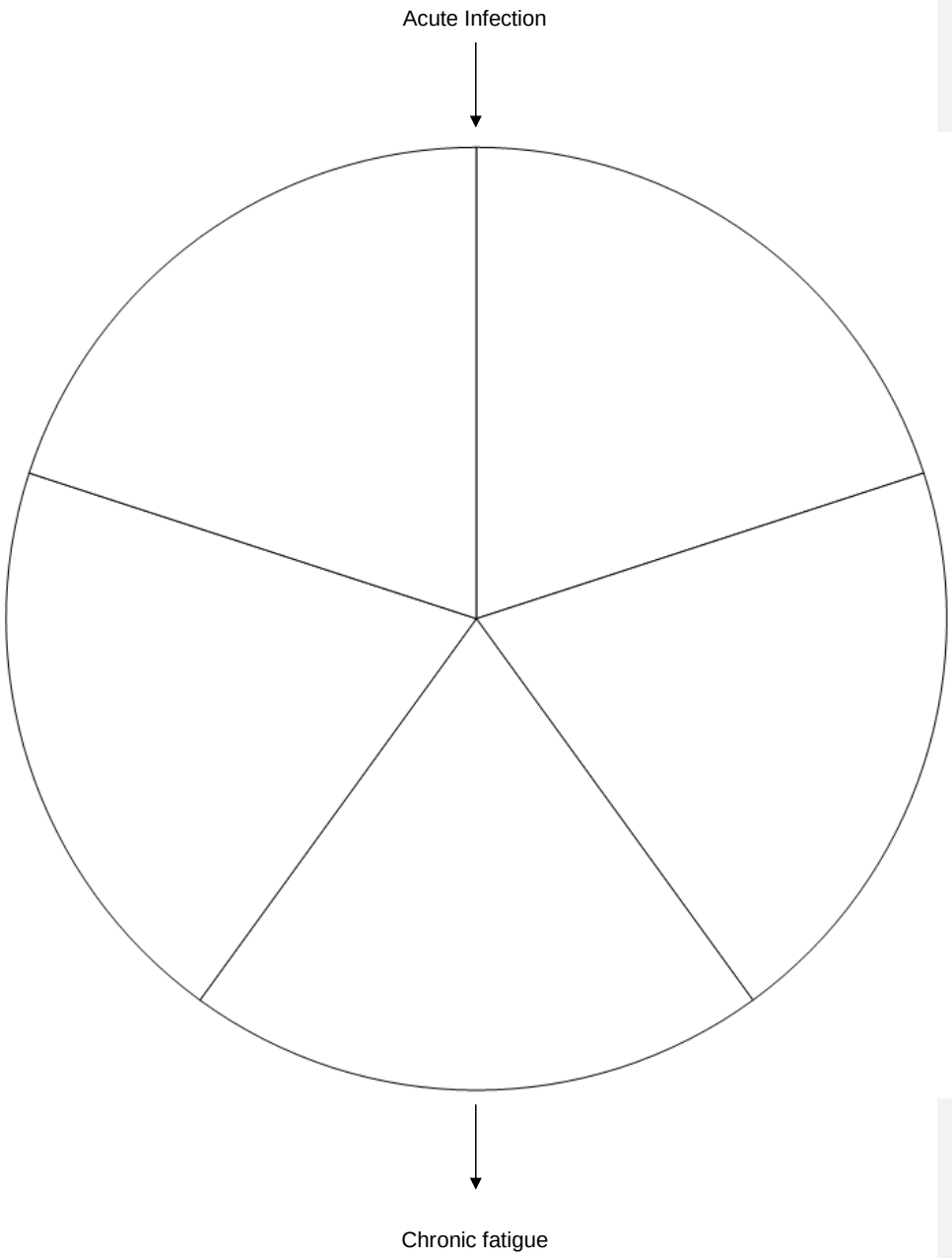
Acute Infection
Chronic fatigue

Figure 2: A summary of the biopsychosocial variables shown to be potential risk factors for persistent post-infectious fatigue up to six months.

Note*: Risk factors in **bold are those factors that were associated with persistent fatigue across time-points in the six-month trajectory, or those which were duplicated across studies. Those not in bold were mixed findings. Such discrepancies could be explained by different infectious illnesses, study characteristics (e.g. sample size, sample population, quality), statistical analyses (e.g. univariate versus multivariate), measures used (e.g. self-report versus objective measures) or fatigue measurement factors (e.g. definition, time-point). Evidence for risk factors marked with ˜ was very variable.

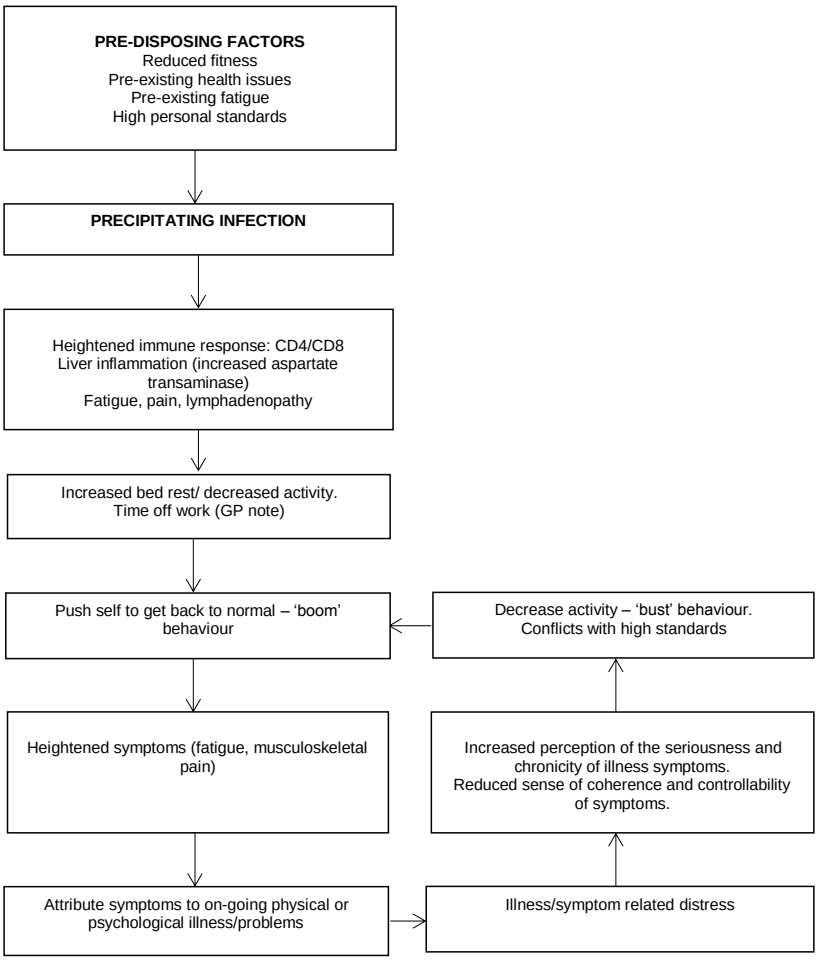

Figure 3: A hypothetical vicious cycle of interacting risk factors for fatigue.

Appendix A: Search terms by database

PsycINFO

exp Prospective Studies/ or prospective.mp.
exp Longitudinal Studies/ or longitudinal.mp.
risk factors.mp. or exp Risk Factors/
risk variables.mp.
exp At Risk Populations/ or risk.mp.
exp Prediction/ or predict$.mp.
exp Cohort Analysis/ or cohort.mp.
cohort study.mp.
exp Followup Studies/ or follow up.mp.
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
("postviral" or "post-viral" or "post viral").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
("postinfect$" or "post-infect$" or "post infect$").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
Infectious Mononucleosis.mp.
mononucleosis.mp.
glandular fever.mp.
("epstein barr" or "epstein-barr" or "EBV").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
exp Epstein Barr Viral Disorder/ or Epstein Barr virus.mp.
"epstein barr virus infection".mp.
("Q-fever" or "Q fever" or "Qfever").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
Coxiella burnetii.mp.
Ross River virus.mp.
viral meningitis.mp.
viral hepatitis.mp.
11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
exp Fatigue/ or exp Chronic Fatigue Syndrome/ or fatigue.mp.

chronic fatigue.mp.
exp Encephalomyelitis/ or myalgic encephalomyelitis.mp.
encephalomyelitis.mp.
prolonged fatigue.mp.
persistent fatigue.mp.
exp Asthenia/ or asthenia.mp.
(tired$ or exhaust$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
(weary or weariness or weakness).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
((loss or lost or lack) adj2 energy).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
(feeling adj2 (drained or sluggish or weak)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
(sleepy or sleepiness or drowsy or drowsiness).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
(apathy or apathetic or lassitude or lethargic or lethargy).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
delayed recovery.mp.
fail$ to recover.mp.
"post viral fatigue syndrome".mp.
convalesence.mp.
mental fatigue.mp.
muscle fatigue.mp.
25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
10 and 24 and 44

EMBASE

exp prospective study/ or prospective.mp.
exp longitudinal study/ or longitudinal.mp.
risk factors.mp. or exp risk factor/
risk variables.mp. or exp risk/
exp high risk population/ or at risk populations.mp.
exp cohort analysis/ or exp follow up/ or cohort.mp.
cohort study.mp.
exp prediction/ or predict$.mp.
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
("postviral" or "post-viral" or "post viral").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
("postinfect$" or "post-infect$" or "post infect$").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Infectious Mononucleosis.mp. or exp mononucleosis/
exp infectious mononucleosis/ or mononucleosis.mp.
glandular fever.mp.
("epstein barr" or "epstein-barr" or "EBV").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Epstein Barr virus.mp. or exp Epstein Barr virus/
"Epstein barr viral disorder".mp.
epstein barr virus infection.mp. or exp Epstein Barr virus infection/
("Q-fever" or "Q fever" or "Qfever").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
Coxiella burnetii.mp. or exp Coxiella burnetii/
Q fever.mp. or exp Q fever/
Ross River virus.mp. or exp Ross River alpha virus/
viral meningitis.mp.

viral hepatitis.mp.
10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
exp postviral fatigue syndrome/ or exp fatigue/ or exp chronic fatigue syndrome/ or exp muscle fatigue/
mental fatigue.mp.
chronic fatigue.mp.
myalgic encephalomyelitis.mp.
exp encephalomyelitis/ or encephalomyelitis.mp.
prolonged fatigue.mp.
persistent fatigue.mp.
astheni$.mp. or exp asthenia/
(tired$ or exhaust$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
(weary or weariness or weakness).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
((loss or lost or lack) adj2 energy).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
(feeling adj2 (drained or sluggish or weak)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
(sleepy or sleepiness or drowsy or drowsiness).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
(apathy or apathetic or lassitude or lethargic or lethargy).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
exp convalescence/ or delayed recovery.mp.
fail$ to recover.mp.
26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41

9 and 25 and 42

Medline

prospective.mp. or exp Prospective Studies/
longitudinal.mp. or exp Longitudinal Studies/
risk factors.mp. or exp Risk Factors/
risk variables.mp.
predict$.mp.
exp Cohort Studies/ or cohort.mp.
cohort analysis.mp.
at risk populations.mp.
follow up.mp.
risk.mp. or exp Risk/
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
("postviral" or "post-viral" or "post viral").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
("postinfect$" or "post-infect$" or "post infect$").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
Infectious Mononucleosis.mp. or exp Infectious Mononucleosis/
mononucleosis.mp. or exp Epstein-Barr Virus Infections/
glandular fever.mp.
("epstein barr" or "epstein-barr" or "EBV").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
Epstein Barr virus.mp.
"Epstein barr viral disorder".mp.

("Q-fever" or "Q fever" or "Qfever").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
Coxiella burnetii.mp. or exp Coxiella burnetii/
Ross River virus.mp. or exp Ross River virus/
viral meningitis.mp. or exp Meningitis, Viral/
exp Hepatitis, Viral, Human/ or viral hepatitis.mp.
12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
exp Fatigue/ or exp Muscle Fatigue/ or exp Mental Fatigue/ or exp Fatigue Syndrome, Chronic/ or fatigue.mp.
"chronic fatigue".mp.
myalgic encephalomyelitis.mp.
exp Encephalomyelitis/ or encephalomyelitis.mp.
prolonged fatigue.mp.
persistent fatigue.mp.
exp Asthenia/ or asthenia.mp.
(tired$ or exhaust$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(weary or weariness or weakness).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
((loss or lost or lack) adj2 energy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(feeling adj2 (drained or sluggish or weak)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

(sleepy or sleepiness or drowsy or drowsiness).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
(apathy or apathetic or lassitude or lethargic or lethargy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
delayed recovery.mp.
fail$ to recover.mp.
"post viral fatigue syndrome".mp.
convalesence.mp.
26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
11 and 25 and 43

Appendix B: Quality Assessment Tool

Effective Public Health Practice Project – modified from intervention to observation focussed

A. SELECTION BIAS

1. Are the individuals selected to participate in the study likely to be representative of the target population?
    a. Very likely
    b. Somewhat likely
    c. Not likely
    d. Can't tell
2. What percentage of selected individuals agreed to participate?
    a. 80-100% agreement
    b. 60-79% agreements
    c. Less than 60% agreement
    d. Not applicable
    e. Can't tell
3. Are the characteristics of the patients included in the study clearly described?
    In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.
    a. Yes
    b. No
4. Were there important differences between those who did and did not participate?
    a. Yes
    b. No
    c. Can't tell

(Examples of confounders: race, sex, marital status/family, age, SES (income or class), education, health status)

B. STUDY DESIGN

1. Indicate the study design.
    a. Randomized controlled trial
    b. Controlled clinical trial
    c. Cohort analytical (two group pre + post)
    d. Case-control
    e. Cohort (one group pre + post – before and after)
    f. Interrupted time series
    g. Other. Specify .....
    h. Can't tell
2. Was exposure biologically verified?
    a. Yes
    b. No
3. Was apriori/theoretical justification of predictors described, and then also mirrored in results section?
    a. Yes
    b. No
    c. Can't tell

C. **CONFOUNDERS**

1. Were there important differences between cases and non-cases when outcome was measured?
    a. Yes
    b. No
    c. Can't tell

Commented [k1]: Additional question. Taken from Q3 Downs & Black (1998) checklist.

Commented [k2]: Duplicated and adapted from C Q1 - Were there important differences between groups prior to the intervention?

Commented [k3]: B Q2 from EPHPP not applicable - Was the study described as randomised?
Replaced based upon Newcastle Ottawa Cohort Scale – Selection Q3

Commented [k4]: Additional question based upon recommendations from Candy et al. (2002) systematic review.

Commented [k5]: Adapted from EHPHH C Q1. Original question: Were there important differences between groups prior to the intervention?

(Examples of confounders: race, sex, marital status/family, age, SES (income or class), education, health status, pre-intervention score on outcome measure)

2. If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis).
    a. 80-100% (most)
    b. 60-79% (some)
    c. Less than 0% (few or none)
    d. Can't tell

D. **BLINDING**

1. Was (were) the outcome assessor(s) aware of the exposure status of participants?
    a. Yes
    b. No
    c. Can't tell
2. Were the study participants aware of the research question?
    a. Yes
    b. No
    c. Can't tell

E. **DATA COLLECTION METHODS**

1. Were data collection tools shown to be valid?
    a. Yes
    b. No
    c. Can't tell
2. Were data collection tools shown to be reliable?
    a. Yes
    b. No
    c. Can't tell
3. Was fatigue measured as the primary outcome?
    a. Yes
    b. No
    c. Can't tell
4. Was the follow-up time period adequately explained?
    a. Yes .....
    b. No

F. **WITHDRAWALS AND DROPOUTS**

1. Were withdrawals and dropouts reported in terms of numbers and/or reasons per group?
    a. Yes
    b. No
    c. Can't tell
    d. Not Applicable (i.e. on time surveys or interviews)
2. Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest).
    a. 80-100%
    b. 60-79%
    c. Less than 60%
    d. Can't tell
    e. Not Applicable (i.e. retrospective case-control)
3. Were there important differences between completers and dropouts?
    d. Yes
    e. No
    f. Can't tell

Commented [k6]: Include patients themselves as self-report

Commented [k7]: D Q1 from EHPHH (omitted: aware of 'the intervention or' exposure…)

Commented [k8]: Additional Q – Focus of study.

Commented [k9]: Additional question: based on Newcastle Ottawa Cohort Scale – Outcome Q2

Commented [k10]: Additional question – investigate attrition bias

(Examples of confounders: race, sex, marital status/family, age, SES (income or class), education, health status, pre-intervention score on outcome measure)

G. **ANALYSES**

1. Are the statistical methods appropriate for the study design?
    a. Yes
    b. No
    c. Can't tell

Commented [k11]: Section G: 'Intervention Integrity' from EHPHH not applicable so omitted.
H Q1, Q2 and Q4 from EPHPP omitted as not relevant:
1.Indicate the unit of allocation (circle one) : community, organisation/institution, practice/office, individual.
2. Indicate the unit of analysis (circle one) : community, organisation/institution, practice/office, individual.
4. Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

Appendix C: Study characteristics and significant statistical outcomes

Study	Infection	Participants (N, % female, mean age, setting, country)	Follow up %	Design and Statistical method	Analysed variables - prospective - measured in relation to fatigue outcome	Fatigue outcome - method - measure	Fatigue measurement time points	Significant statistical outcomes
Candy et al. 2003	IM (positive IM serology)	N = 71 60% female Mean age = 22.9 (s.d. = 8.2) Three haematology and two virology labs, six general practices and a student healthcare centre. Country: UK	3 months: 69% 6 months: 87% 12 months: 70%	Prospective cohort Mann-Whitney U-test Univariate Logistic regression OR	Risk factor variables: activated CD4 and CD8 cytotoxic T cells, cortisol concentration, cortisol concentration change baseline - 6 months, more than one recent adverse life event, childhood experience of illness in family, past history of emotional problems, doing regular sport, 10+ days off sick, 'recovered' at interview, given advice to rest by GP, high total symptom, high symptoms severity, low physical functioning, poor physical functioning in last month, poor emotional functioning in last month, poor functioning on Work and Social Adjustment Scale (WSAS), GHQ-12>5 (psychological distress), low control/cure (IPQ), high consequences (IPQ), expect recovery will take >1 month.	Questionnaire Chalder Fatigue Scale	baseline, 3 months, 6 months, 12 months	Fatigue at 3 months was associated with higher acute phase % of activated CD4 (U=5.0, p=.02) and activated CD8 (U=7.0, p=0.039). All the following are significant at p<.05: Fatigue at 3 months was also associated with high total symptom (OR 8.6, 95% CI 2.0-37), high symptom severity (OR 12, 95% CI 2.8-52), low physical functioning (OR 4.5, 95% CI 1.3-15), poor physical functioning in last month (OR 6.7, 95% CI 1.6-28), poor functioning on WSAS (OR 20, 95% CI 3.8-1.4 [sic]), GHQ-12>5 (OR 11, 95% CI 2.7-42), high consequences (OR 5.8, 95%CI 1.6-20) and expect recovery will take >1 month (OR 8.4, 95% CI 2.0-36). Fatigue at 6 months was associated with GHQ-12>5 (OR 2.8, 95% CI 1.0-8.1), high consequences (OR 3.0, 95% CI 1.0-9.0) and expect recovery will take >1 month (OR 3.4, 95% CI 1.1-11). Fatigue at 12 months was associated with high total symptom (OR 5.7, 95% CI 1.4-24) and poor functioning on WSAS (OR 6.5, 95% CI 1.5-27).
Cope et al. 1994	'viral illness' (diagnosis)	N = 618 63.5% female Mean age Male = 29.20 (s.d.= 7.7) Female = 30.15 (s.d.= 7.7) Setting: 42 general practices Country: UK	81.20%	Prospective cohort t-test Logistic regression OR	Risk factor variables: GP sick note, GP diagnosis, medication, previral fatigue, symptoms, virus beliefs, GHQ-3 score (psychological distress), attributional style (psychologising, somatising, normalising)	Questionnaire Fatigue Questionnaire (David et al., 1990)	6 months	Fatigue at 6 months was associated with receiving a sick note during infection (OR 1.68, 95% CI 1.05-1.54, p=.01), less certain diagnosis of viral illness (X2=19.26, p=.02), GHQ-3 scores at initial presentation (p=.004), higher psychologising attribution scores (p<.05), higher somatising attribution scores (p<.05), lower normalising attribution scores (p<.05), belief that catch virus when rundown or under stress (sub-scale) (t=3.02, p=.003).

Cope et al. 1996	'viral illness' (diagnosis)	N = 128, Cases N=64, 78% female, mean age = 30.5 (s.d. = 6.5) Controls N = 64, 78% female, mean age = 31.4 (s.d. = 7.3) Setting: General practice Country: UK	78%	Prospective cohort (case-control) Logistic regression OR	Risk factor variables: GHQ-3 score (psychiatric morbidity), attributional style, sick certification, presence of fatigue (at time of viral illness), past psychiatric history (verified by GP records).	Interview CFS (Oxford criteria)	6 months	CFS at 6 months was associated with sick certification (p=.002, OR 8.5, CI 4.2-17.2), a psychological symptom attributional style (p=.007, OR 2.1, CI 1.6-2.7) and presence of fatigue at time of viral illness (p=.05, OR 6.4, CI 2.5-16.4).
Hickie et al. 2006	EBV, Q fever, RRV (positive serology tests)	N = 253 43% female Mean age = 34 (16-77) Setting: Family practitioner practices, four diagnostic pathology laboratories Country: Australia	90.5%	Prospective cohort Stepwise multiple regression - standardised beta co-efficient	Risk factor variables: acute sickness, irritability, musculoskeletal pain, mood disturbance, neurocognitive disturbance, fatigue, premorbid psychiatric disorder, intercurrent psychiatric disorder, neuroticism score, locus of control score	Questionnaire SOMA subscale of SPHERE Interview CFS (CDC criteria)	3 months, 6 months, 12 months	Fatigue at 3 months was associated with irritability (b=0.24, p<.05), musculoskeletal pain (b=0.27, p<.05), neurocognitive disturbance (b=0.24, p<.05) and fatigue (b=0.50, p<.001). CFS at 6 months was associated with musculoskeletal pain (b= 0.30, p<.05) and fatigue at baseline (b= 0.35, p<.001). CFS at 12 months was associated with fatigue at baseline (b= 0.27, p<.05)
Hotopf et al. 1996	acute onset viral meningitis (clinical diagnosis) (controls - other viral diagnoses)	N = 159 (83 patients, 76 controls) Cases 64% female Controls 46% female Mean ages: 32 and 31 Setting: Four virology laboratories and specialist hospitals. Country: UK (?)		Prospective case-control Logistic regression OR (adjusted)	Risk factor variables: psychiatric history	Questionnaire Chalder Fatigue Scale CFS (Oxford criteria, CDC criteria)	6-24 months post onset (mean = 18 months)	Psychiatric history was a risk factor for CFS (Oxford criteria) (OR 3.58, 95% CI 1.2-10.6, p=.02) and CFS (CDC criteria) (OR 7.82, 95% 1.8-34.3, p=.006), but not chronic fatigue (as measured on the Chalder Fatigue Scale) (OR = 1.33, 95% CI 0.5-3.4, p=.55).

Huang et al. 2010	IM (positive monospot lab records)	N = 301 CFS N=39, 89.7% female Controls N=39 'adolescents' Setting: clinical care sources e.g. school clinics, paediatric practices, virology lab of hospital. Country: USA Same cohort as Katz et al. (2009)		Prospective cohort (case-control) t-test Compare CFS cases v controls	Risk factor variables: (measured for 'before' and 'during mono'): Physical Activity: 20-Minute hard exercise, 20-Minute light exercise, Television/video/computer, Sleep, Napping, Other sedentary activity. Fatigue severity at baseline.	Interview CFS (CDC criteria - revised by Jason et al. 2006)	6 months	CFS at 6 months was associated with fatigue severity at baseline, t(39)=3.70, p<.001.
Jason et al. 2014	IM (positive monospot test)	N = 301 CFS: N = 39, 89.7% female, mean age = 16.09 (1.4), 87.2% Caucasian Controls: N = 50, 74% female, mean age = 16.1 (1.5), 94% Caucasian Setting: clinical care sources e.g. school-based health clinics. Country: USA Same cohort as Katz et al. (2009)	53 of 70 'not recovered' =75.7% 39/53 classified as CFS.	Prospective cohort (case-control) Logistic regression b, Wald X^2, OR.	Risk factor variables: autonomic symptoms, perceived stress score, life events score, family stress (around or prior to mono onset?, continuing?, since mono any family stress?, continuing?), days spent in bed, days of school missed, hard time attending school regularly?, difficulties with concentrating, learning or remembering, at least one current psychiatric diagnosis, total number of current diagnoses received.	Interview CFS (Jason et al. (2006) revision of the CDC criteria)	6 months	CFS at 6 months was associated with autonomic symptoms (b=.14, X^2=22.23, OR 1.15, p<.001), perceived stress (b=.10, X^2=9.81, OR 1.10, p<.001), life events (b=.60, X^2=13.14, OR 1.83, p<.001), days spent in bed (b=.08, X^2==5.98, OR 1.08, p=.01), days of school missed (b=.09, X^2=5.89, OR 1.09, p=.01), at least one current psychiatric diagnosis (b=1.39, X^2=9.28, OR 4.00, p<.001) and total number of current diagnoses received (b=.68, X^2=5.13, OR 1.97, p=.02).

Katz et al. 2009	IM (positive monospot test)	N = 301 CFS N=39, 90% female Controls N=50 'adolescents' Setting: clinical care sources e.g. school clinics, pediatric practices, virology lab of hospital. Country: USA	53 of 70 'not recovered' =75.7% 39/53 classified as CFS.	Prospective cohort (case-control) Fisher's exact test *X*2	Risk factor variable: prescribed steroid treatment during acute episode of mononucleosis.	Interview CFS (CDC criteria - revised by Jason et al., 2006) (Questionnaire Chalder Fatigue Scale)	6 months, 12 months, 24 months	none
Kremers et al. 2014	Q-fever (positive serology)	N = 102 35.3% female Mean age = 48 (s.d. = 16) Setting: Microbiology & Infection Control Hospital Department. Country: Netherlands	70.70%	Prospective cohort Mann Whitney U test	Risk factor variables: interleukin-6 and C-reactive protein levels.	Questionnaire Nijmegen Clinical Screening Instrument: fatigue sub-domain	4 years after diagnosis	none.

Löwe et al. 2014	Shiga Toxin-Producing Escherichia coli 0104 (STEC) (clinical diagnosis)	N = 389 69% female Mean age = 46 (s.d. = 17) Setting: 13 hospitals Country: Germany	79%	Prospective cohort Multiple linear regression	Risk factor variables: prior psychiatric disorder, prior traumatic event, diarrhoea in the past 4 months, pre-existing chronic condition (e.g. IBS, fibromyalgia), neuroticism, pessimism, optimism, self-efficacy, duration of in-patient treatment (weeks), treatment in intensive care unit, haemolytic uremic syndrome, neurological symptoms, more than 4 instances of diarrhoea on 3 or more days, abdominal pain, length of bloody diarrhoea, fever, fear of death, social support.	Questionnaire Chalder Fatigue Scale (validated German version) (Martin et al., 2010)	6 months ("fatigue persisting for 3 or more consecutive months").	Fatigue at 6 months was associated with pre-existing chronic condition (b = 1.75, 95% CI 0.43-3.07, p=.009), neuroticism (b = 1.22, 95% CI 0.20-2.23, p=.019) and treatment in intensive care unit (b = 1.73, 95% CI 0.03-3.43, p=.046).
Moss-Morris et al. 2011	Glandular fever (GF) (positive monospot or serology test)	N = 246 62% female Mean age = 22.8 (s.d. = 8.3) 96% NZ European, 2% Asian, 2% Maori Setting: community clinical diagnostic service. Country: New Zealand	91% - 3 months 88% - 6 months	Prospective cohort (case-control) Independent sample t-tests and X^2 tests. Individual logistic regression OR.	Risk factor variables: mean GF symptoms, mean non-GF symptoms, doctor's advice to rest, doctor's advice to avoid exercise, doctor's advice to take medication, perceived stress, negative perfectionism, anxiety, depression, illness identity, timeline, consequences, personal control, illness coherence, emotional representations, all-or-nothing behaviour, limiting behaviour.	Questionnaire CFS (CDC or Oxford criteria)	3 months 6 months	Fatigue at 3 months was associated with non-GF somatic symptoms (t(222) = -4.51, p<.001), anxiety (OR 1.22, 95% CI 1.08-1.38, p=.002), depression (OR 1.26, 95% CI 1.09-1.46, p=.002), illness identity (OR 1.17, 95% CI 1.01-1.35, p=.03), timeline (OR 1.3, 95% CI 1.09-1.54, p=.004), consequences (OR 1.15, 95% CI 1.02-1.29, p=.03), personal control (OR 0.86, 95% CI 0.75-0.98, p=.02), illness coherence (OR 0.75, 95% CI 0.62-0.92, p=.01), emotional representations (OR 1.17, 95% CI 1.06-1.29, p=.002), all-or-nothing behaviour (OR 1.13, 95% CI 1.03-1.24, p=.01). CFS at 6 months was associated with non GF somatic symptoms (t(215) = -2.19, p=.03), negative perfectionism (OR 1.08, 95% CI 1.01-1.16, p=.04), anxiety (OR 1.18, 95% CI 1.03-1.34, p =.02), depression (OR 1.26, 95% CI 1.06-1.50, p=.01), timeline (OR 1.38, 95% CI 1.11-1.72, p=.004), illness coherence (OR 0.77, 95% 0.62-0.95, p=.01), emotional representations (OR 1.11, 95% CI 1.00-1.24, p=.05), all-or-nothing behaviour (OR 1.14, 95% CI 1.02-1.26, p=.02).

Petersen et al., 2006	IM (positive antibody test) (2 comparative cohorts - influenza and tonsillitis)	N=1438 (1318 not including pre-morbid fatigue). Median age = 19 years Setting: General practices (General Practice Research Database). Country: UK	n/a	Prospective cohort (matched, historic) Univariate regression OR Multivariable logistic regression	Risk factor variables: lymphadenopathy within 2 months of positive test, number of GP consultations in year before onset, number of sickness certificates in the year before onset, premorbid anxiety or depressive (mood) disorder, premorbid fatigue, premorbid atopy (eczema, asthma or hay fever).	Database codes: Fatigue symptoms and diagnoses	Fatigue: in year after onset (median = 55 days)	Fatigue after IM was associated with premorbid fatigue (OR 2.0, 95% CI 1.2-3.1, p=.004), 3+ GP consultations in the year before IM (OR 1.7, 95% CI 1.2-2.3, p=.002) and premorbid mood disorder (OR 2.6, 95% CI 1.4-4.8, p=.002).
Schur et al. 2007	IM (positive monospot test)	N = 150 53% female Mean age = 21.3 (s.d. = 6.7) 90% Caucasian Setting: Health maintenance organisation. Country: USA	95%	Prospective cohort Logistic Regression OR (unadjusted and adjusted)	Risk factor variables: BMI at baseline, weight change from baseline to 6 months	Questionnaire 4-item vitality subscale of Medical Outcomes SF-36 health survey	baseline, 6 months	none
Seet et al. 2007	Dengue infection (serologically confirmed)	N = 127 44.1% female Mean age=36.06 (s.d.=13.722) 75.6% Chinese, 17.3% Malay, 4.7% Indian Setting: Hospital Country: Singapore	100%	Prospective cohort Multivariate logistic regression OR	Risk factor variables: Symptoms: fever, nausea, chills, poor appetite, fatigue, cough, abdominal pain, vomiting, diarrhoea, rashes, muscle pain, headaches. Laboratory parameters: (concentrations of…) White cell count, haemoglobin, haematocrit, platelet, sodium, potassium, urea, creatinine, albumin, total bilirubin, aspartate transaminase, alkaline transaminase, alkaline phosphatase, lactate dehydrogenase. Prothrombin time, activated thromboplastin time. Dengue severity (dengue haemorrhagic fever)	Questionnaire Chalder Fatigue Scale	2 months following hospitalisation	Fatigue 2 months after infection was associated with: presence of chills (OR 6.904, 95% CI 1.157-41.202, p=.034) and absence of rashes (OR 0.113 95% CI 0.017-0.774, p=.026).

van Loenhout et al. 2015	Q-fever 'lab confirmed'	N = 336 48.5 % female Mean age = 48.5 (s.d. = 13.9) 98.5 % Dutch Setting: Municipal Health Services Country: Netherlands	82.74%	Prospective cohort Multivariate regression	Risk factor variables: pre-existing health problems, diagnosis during the acute Q-fever episode.	Questionnaire Nijmegen Clinical Screening Instrument: fatigue sub-domain	12 and 24 months	Pre-existing health problems were associated with fatigue at 12 months, b = 4.45, CI 0.79 - 8.10, p=.017, and 24 months, b = 7.41, CI 3.65 - 11.17, p<.001.
Wessley et al. 1995	General infections	N=1167 of 1199 exposed, 68% female, mean age = 32.7 (s.d.=7.5) N=671 from exposed cohort with complete data from all stages. Setting: Community sampling. General practices Country: UK	84%	Prospective cohort (cohort and case-control) X^2 Independent regression OR	Risk factor variables: pre-onset fatigue, pre-onset psychological distress, psychological distress at time of infection, belief that fatigue at presentation was due to a physical cause, viral symptoms, local symptoms.	Questionnaire Fatigue Scale (Chalder)	Community screening, baseline, 6 months	Fatigue at 6 months was associated with premorbid fatigue (OR 3.0, 95% 1.9-4.7, p<.001), pre-onset psychological morbidity (OR 1.8, 95% CI 1.2-2.9, p=.009), psychological morbidity at time of infection (OR 1.8, 95 CI, p=.01) and higher number of general viral symptoms (no data).

White et al. 2001	IM (positive monospot and 10%+ atypical lymphocytes) and non-IM (other diagnosed infections) (upper respiratory tract infection comparison group)	N = 250 (118 IM, 127 non-IM, 5 excluded) 51% female Setting: City University, London. St Bartholomew's Hospital, London General surgeries Country: UK		Prospective cohort Stepwise logistic regression; Univariate Relative Risk	Risk factor variables: cervical lymphadenopathy, atopy, AST at 1 month, yGT at 1 month, bilirubin at 1 month, fatigue at onset, time in bed at onset, exercise power, fitness, GP attendance in year before onset, premorbid psychiatric disorder (PPD) at any time, PPD in year before onset, PPD in 2 weeks before onset, GP record of PPD, GP record of any PPD treatment, premorbid mood disorder (PMD) at any time, PMD in year before onset, PMD in 2 weeks before onset, GP record of PMD, depression at 1 month, anxiety at 1 month, self-rated extroversion, relative rated extroversion, self-rated emotionality, relative-rated emotionality	Interview Empirically defined fatigue syndrome (White et al., 1995). CFS: Oxford criteria CDC criteria	1, 2, 6 months after symptom onset. Primary care records examined 2.5 years later.	Fatigue at 2 months was associated with cervical lymphadenopathy (RR 4.9, CI 2.5-9.7), AST at 1 month (RR 2.4, 95% CI 1.3-4.5), fatigue at onset (RR 2.0, 95% CI 1.3-3.0), time in bed at onset (RR 2.0, 95% CI 1.2-3.2), lower fitness (RR 0.6, 95% CI 0.4-1.0). Fatigue at 6 months was associated with AST at 1 month (RR 2.3, 95% CI 1.0-4.8), fatigue at onset (RR 2.1, 95% CI 1.0-4.3), lower fitness (RR 0.4, 95% CI 0.2-0.9), GP record of PMD (RR 2.1, 95% CI 1.0-4.4), depression score (RR 2.1, 95% CI 1.0-4.5). CFS (Oxford criteria) at 6 months was associated with time in bed at onset (RR 3.2, 95% CI 1.5-7.1), lower fitness (RR 0.4, 95% CI 0.2-0.9), GP attendance in year before onset (RR 4.1, 95% CI 1.7-10.3), GP record of PPD (RR 4.0, 95% CI 2.2-7.4), GP record of any PPD treatment (RR 3.7, 95% CI 2.0-6.8), PMD at any time (RR 2.1, 95% CI 1.2-3.8), PMD in 2 weeks before onset (RR 2.9, 95% CI 1.5-5.6), GP record of PMD (RR 3.5, 95% CI 2.0-6.3), anxiety score (RR 3.9, 95% CI 1.4-11.0), mood disorder at 2 months (RR 4.4, 95% CI 2.6-7.5), self-rated emotionality (RR 1.9, 95% CI 1.0-3.5, $p<.05$), relative-rated emotionality (RR 2.3, 95% CI 1.2-4.2). CFS (CDC criteria) at 6 months was associated with time in bed at onset (RR 2.2, 95% CI 1.1-4.6), lower fitness (RR 0.5, 95% CI 0.2-1.0), GP attendance in year before (RR 3.0, 95% CI 1.3-7.0), GP record of PPD (RR 2.3, 95% CI 1.2-4.6), PMD at any time (RR 2.2, 95% CI 1.2-3.9), PMD in 2 weeks before onset (RR 2.8, 95% CI 1.4-5.8). $p<.05$ for all.

Table 3: Summary of biological factors shown to be significantly associated with the development of persistent fatigue at at least one time-point.

		Biological								
		Haematological & biochemical parametres		*Individual symptoms during acute illness*		*Number of acute symptoms*		*Severity of acute symptoms*	*Pre-existing health issues*	
		CD4/CD8	AST	Fatigue	Other individual symptoms	General	Illness specific		Fatigue	General health
Total number of studies		1	2	5	9	3	2	4	3	2
Sub-acute		1/1	1/2	2/3	mixed*	2/2	0/1	1/2	1/1*	
6 months	chronic	0/1	1/1	1/1	mixed	1/2	0/1	1/3	1/2	1/1
	CFS (any diagnostic criteria)		0/1	3/4	mixed	1/1	0/1			
Long term				1/1	mixed	1/1		1/1		1/1

*Includes Petersen et al. (2006). Fatigue measured in 'year after onset' through database search of diagnoses and symptoms. Median = 55 days, therefore, included as sub-acute.

Note: In this table, and the following ones, the ratios denote the number of papers which report each respective risk factor as significant, out of the number of papers which investigated it as a risk factor.

Table 4: Summary of social factors shown to be significantly associated with the development of persistent fatigue at at least one time-point.

		Social		
		Adverse events	*GP interactions*	
			sick note	uncertain diagnosis
Total number of studies		3	2	1
Sub-acute		0/1		
6 months	chronic	0/2	1/1	1/1
	CFS (any diagnostic criteria)	1/1	1/1	
Long term		0/1		

Table 5: Summary of behavioural factors shown to be significantly associated with the development of persistent fatigue at at least one time-point.

		Behaviour					
		All-or-nothing behaviour	*Limiting behaviour*		*Previous GP attendance*	*General functioning* (reduced)	*Physical functioning/fitness* (reduced)
			Other	Bed-rest			
Total number of studies		1	3	2	2	2	2
Sub-acute		1/1	0/2	1/1	1/2*	1/1	2/2
6 months	chronic		0/1	0/1	0/1	0/1	1/2
	CFS (any diagnostic criteria)	1/1	1/2	2/2	1/1	0/1	1/1
Long term			0/1			1/1	0/1

*Includes Petersen et al. (2006). Fatigue measured in 'year after onset' through database search of diagnoses and symptoms. Median = 55 days, therefore, included as sub-acute.

Table 6: Summary of cognitive factors shown to be significantly associated with the development of persistent fatigue at at least one time-point.

		Cognitive								
		Individual traits	*Illness specific perceptions*							
		Neuroticism	Negative perfectionism	Perceived stress	Attributional style	Identity	Timeline	Consequences	Control	Illness coherence (low)
Total number of studies		3	1	2	2	1	2	2	2	1
Sub-acute		0/2	0/1	0/1		1/1	2/2	2/2	1/2	1/1
6 months	chronic	1/2			1/1		1/1	1/1	0/1	
	CFS (any diagnostic criteria)	1/2	1/1	1/2	1/1	0/1	1/1	0/1	0/1	1/1
Long term		0/1					0/1	0/1	0/1	

Table 7: Summary of emotional factors shown to be significantly associated with the development of persistent fatigue at at least one time-point.

		Emotional					
		Anxiety	*Depression*	*Distress*		*Psychiatric diagnoses*	*Pre-morbid (pre-infection) distress*
				General	Illness related		
Total number of studies		2	2	4	1	2	8
Sub-acute		1/2	1/2	1/1	1/1	0/2	1/4*
6 months	chronic	0/1	1/1	3/3			2/4
	CFS (any diagnostic criteria)	2/2	1/2	0/1	1/1	1/2	1/3
Long term				0/1		0/1	1/3**

*Includes Petersen et al. (2006). Fatigue measured in 'year after onset' through database search of diagnoses and symptoms. Median = 55 days, therefore, included as sub-acute.

**Includes Hotopf et al. (1996). Fatigue time-point was 6-24 months. Mean = 18 months, therefore, included as long term.

Table 8: Summary of ratings for each study across the quality domains

	Selection Bias	**Study Design**	**Confounders**	**Blinding**	**Data Collection**	**Withdrawals/ Dropouts (participant follow-up)**	**Overall rating**	
Candy et al. (2003)	2/3	1	2	2	1	2	2	moderate
Cope et al. (1994)	1/2	3	2	2	2	1	2	moderate
Cope et al. (1996)	2	3	1	2	2	2	2	moderate
Hickie et al. (2006)	2/3	2	1	2	1	3	2	moderate
Hotopf et al. (1996)	2	2	1	2	3	2	2	moderate
Haung et al. (2010) *Referenced Katz et al. for study details*	2	2	1	1	1	3	1/2	strong-moderate
Jason et al. (2014)	2	2	2	1	1	2	2	moderate
Katz et al. (2009)	2	2	3	1	2	2	2	moderate
Kremers et al. (2014)								
Loewe et al. (2014)	2	2	3	2	1	2	2	moderate
Moss-Morris et al. (2011)	2/3	1	1	2	1	1	1/2	strong-moderate
Peterson et al. (2006)	1	2	1	2	3	2	2	moderate
Schur et al. (2007)	2/3	2	1	2	2	3	2	moderate
Seet et al. (2007)	3	2	3	2	2	1	2/3	moderate-weak
van Loenhout et al. (2015)	1	2	3	2	2	1	2	moderate
Wessely et al. (1995)	2	3	1	2	1	1	1/2	strong-moderate
White et al. (2001)	2/3	2	1	1	2	2	2	moderate

Key: 1= strong, 2= moderate, 3= weak